REMARKS

Claims 36-54 are pending. Claims 28-35 are cancelled as being drawn to a non-elected invention. Claims 37 and 55 are cancelled to expedite prosecution. Applicants reserve the right to pursue the subject matter of Claims 37 and 55 in another application. In the present amendment, Claims 36-54 are amended for clarity. Claims 38-54 are further amended to have proper antecedent basis with the claims from which they depend.

The claim amendments are presented in a revised format per the USPTO's announcement 'Amendments in a Revised Format Now Permitted', signed 31 January 2002, and accordingly do not conform to the current reading of 37 C.F.R. §1.121, which Applicants understand has been waived. Accordingly, a complete listing of all claims that are, or were in the application, along with an appropriate status identifier, is provided above in the section entitled "Amendments to the Claims". Markings are provided on claims amended in the present amendment.

Amendments to the drawings are discussed below.

Drawings:

Figure 1A is amended to correct an obvious error. In accordance with 37 C.F.R. § 1.121(d), Applicants enclose herein a separate paper showing the proposed changes in red for approval by the Examiner and a new formal drawing in compliance with 37 C.F.R. §§ 1.84, 1.85. In amended Figure 1A, the "hook up wire" and "ultra fine platinum wire" are indicated by reference numbers 4 and 2, respectively. Support for these amendments is found at page 12, lines 19-24.

In response to "Notice of Draftsperson Patent Drawing Review" (PTO-948) mailed November 6, 2001, Applicants enclose herein formal drawings of Figures 1-14.

Rejection under 35 U.S.C. § 103(a):

Claims 36-55 stand rejected as being obvious over Heller, *et al.*, U.S. Patent No. 5,632,957, in view of Guttman, *et al.*, U.S. Patent No. 5,662,787, and Anderson, *et al.*, U.S. Patent No. 6,168,948. Applicant's respectfully traverse.

Heller, *et al.* disclose electronic devices for performing biological procedures, such as, nucleic acid hybridization, in microscopic formats (column 4, lines 48-59). "The basic device

has a matrix of addressable microscopic locations on its surface . . . . All micro-locations can be addressed with their specific binding entities" (column 4, lines 62-67). Hybridized DNAs are detected by a "flourescent dye detection process. . ." (column 19, lines 26-42). A simplified version of the hybridization system consists of a substrate, an array of electronically addressable microlocations, a permeation layer, and an attachment layer to provide binding sites for target molecules (column 7, line 66 to column 8, line 15). The permeation layer is generally described to consist of a hydrophilic gel of polyacrylamide and polylysine to provide functional groups for attachment of binding entities (column 15, lines 7-16).

Guttman, *et al.* disclose a method of electrophoretically separating oligosaccharides in a separation medium having a pH of more than about 2.5 and less than about 8.0 (column 6, lines 30-35). Lithium acetate buffer is optionally used to maintain a gel medium of about 0.4% wt % polyethylene oxide at the desired pH (column 3, lines 35-39). The separated oligosaccharides are labeled prior to electrophoresis and detected using a fluorescence detector (column 3, lines 47-50).

Anderson, *et al.* disclose a method of probing a nucleic acid sample using an array of oligonucleotide probes attached to a solid support (column 12, lines 47-49). The solid support contains photosensitive protecting groups which provide discrete hydroxyl groups for oligonucleotide synthesis and attachment (column 13, lines 5-14). Hybridization between a nucleic acid sample and the probe array is detected using a "series of active electrodes . . . and common electrodes . . . positioned proximal to the probes" (column 60, lines 28-30). "[A] shift in the dielectric properties [is detected] at the locations where [a] target sequence binds with the probes" (column 60, lines 36-38). "[T]he electrodes are used to measure . . . impedance proximal [to] a location where binding takes place" (column 60, lines 38-40).

In contrast to these references, Claim 36 of the present invention is drawn to an apparatus for the electrical detection, such as impedance detection, of the interactions of probes and target molecules comprising a substrate comprising a plurality of microelectrodes each comprising a conjugated polymer and an oligonucleotide probe attached thereto. A

voltage source and a detector are connected to the microelectrodes and an electrolyte solution comprising lithium ions is in contact with the microelectrodes.

A rejection under § 103(a) must "present a line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." M.P.E.P. § 2142 (citing *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. Appl. & Inter. 1985). This requires the rationale for the rejection to meet the three basic criteria set forth in M.P.E.P. § 2143:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations.
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> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

"The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness." M.P.E.P. § 2142.

Regarding the limitations of Claim 36, Applicants submit that Heller, *et al.* do not teach or suggest an apparatus for the electrical detection of oligonucleotide probe and target nucleic acid interactions, conjugated polymer film or an electrolyte solution comprising lithium ions in contact with a plurality of microelectrodes. Rather, Heller, *et al.* describe a device the employs functionalized hydrophilic gels in a permeation layer (column 15, lines 3-16) in the fluorescence detection of DNA hybrids (column 19, lines 26-42). In addition, Heller, *et al.* do not teach or suggest the composition of an electrolyte solution employed as a component of their device. In view of these differences, Applicants submit that Heller, *et al.* teach away from electrical detection of nucleic acid interactions and the use of conjugated polymer films, and is silent in regard to the claimed electrolyte solution comprising lithium ions in contact

with a plurality of microelectrodes. *see* M.P.E.P. § 2145. Therefore, Heller, *et al.* cannot support a legal conclusion of obviousness.

Guttman, *et al.* disclose the use of lithium acetate buffer; however, the mere disclosure of lithium acetate is an improper basis for combining Guttman, *et al.* and Heller, *et al.* and cannot overcome the deficiencies of Heller, *et al.* described above. In Guttman, *et al.*, lithium acetate buffer is disclosed in connection with the electrophoresis of oligosaccharides through a gel medium. Therefore, Guttman, *et al.* disclose an electrophoresis device, which is fundamentally distinct from the claimed apparatus. The Guttman, *et al.* device does not comprise the claimed substrate, microelectrodes, conjugated polymer film, oligonucleotide probes, a voltage source connected to microelectrodes, an electrolyte solution comprising lithium ions in contact with microelectrodes, or a detector connected to the microelectrodes. In view of these disparities, Applicants submit that Guttman, *et al.* is nonanalogous art and is not properly cited under § 103(a). Oligosaccharide electrophoresis and fluorescence detection are not the field of Applicants' endeavor and are not reasonably pertinent to an apparatus for the electrical detection of nucleic acid interactions. *see* M.P.E.P. § 2141.01(a) (citing *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992)).

Even assuming *arguendo* that Guttman, *et al.* is analogous art, the disclosure of lithium acetate buffer and a device for the electrophoresis of oligosaccharides does not provide the motivation to combine Guttman, *et al.* and Heller, *et al.*

> 'There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art.' *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without motivation to combine, a rejection based on a *prima facie* case of obviousness was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

M.P.E.P. 21430.01. Recently, the Federal Circuit overturned the Board of Patent Appeals and Interferences' ("Board's") decision to uphold a § 103(a) rejection because "the Board rejected the need for 'any specific hint or suggestion in a particular reference' to support the

combination. . . of references." *In re Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2002). The court further stated that "[t]he factual question of motivation is material to patentability, and cannot be resolved on subjective belief and unknown authority, but must be based on objective evidence of record. . . ." *Id.* at 1343-1344. " 'Common knowledge and common sense,' even if assumed to derive from the agency's expertise do not substitute for authority when the law requires authority." *Id.* at 1345.

In view of these requirements, Applicants submit that the Examiner has not provided objective evidence to support the combination of Guttman, *et al.* and Heller, *et al.* In the Office Action, the Examiner states at paragraph 12 that "Guttman et al., teach at column 6 that the buffer and its pH are important, as is the presence of molecular sieving medium, and that the use of their buffer provides improved quantitative data." However, the use described and the purported improvements are in connection with a device designed for the electrophoresis of oligosaccharides and their detection by fluorescence. This statement does not teach or suggest an apparatus for the electrical detection of nucleic acid interactions. Therefore, Applicants submit that by combining Guttman, *et al.* and Heller, *et al.* the Examiner has not considered Guttman, *et al.* as a whole and has relied on impermissible hindsight analysis to support the combination. *see* M.P.E.P. §§ 2141.02, 2145.

Applicants further submit that Anderson, *et al.* cannot be properly combined with Heller, *et al.* Anderson, *et al.* disclose a device for the detection of nucleic acid hybridization. However, in the device of Anderson, *et al.* the oligonucleotides are not attached to a microelectrode but rather are attached directly to a solid support by photolithographic and solid phase synthesis methods. (column 12, lines 55-58). Anderson, *et al.* further state that the electrodes are "positioned proximal to the probes" (column 60, lines 28-30) rather than being attached to the electrode as disclosed by Heller, *et al.* Therefore, Anderson, *et al.* and Heller, *et al.* cannot properly be combined because

> the "suggested combination of references would required a substantial reconstruction and redesign of the elements shown in [the primary] reference as well as a change in the basic principle under which the [primary reference] construction was designed to operate."

M.P.E.P. § 214.01 (citing *In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349, 352 (CCPA 1959). Applicants further submit that the disclosure of oligonucleotide probes attached proximal to the electrodes is contrary to the claimed apparatus, and, therefore, Anderson, *et al.* teach away from the claimed invention. *see* M.P.E.P. § 2145. Lastly, Anderson, *et al.* do not teach or suggest an electrolyte solution comprising lithium ions in contact with a plurality of microelectrodes.

In view of the above, Applicants submit that the references either alone or any combination thereof do not support a *prima facie* case of obviousness and respectfully request the rejection be withdrawn.

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,
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Date: 4/7/03

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Filed under 37 C.F.R. § 1.34(a)

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